REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims fully supported by the specification and claims as originally filed, and do not add new matter.

Prior to the present amendment, Claims 58-77 were pending in this application. With this amendment, Claims 66-67 and 71-73 have been canceled without prejudice and Claims 58-65, 68-69, and 75-76 have been amended to further clarify what applicants have always regarded as their invention. Support for the amendments to Claims 58-62 can be found, for example, Example 111 on page 327, line 30 to page 328, line 9.

New Claims 78-82 and 83-87 are fully supported by the specification and the claims as originally filed. Support for new Claims 78-82 can be found, for example, under Example 110 on page 327, lines 9-29. Support for new Claims 83-87 can be found, for example, under Example 133 on page 355, line 15 to page 356, line 6.

Claims 58-65, 68-70, and 74-87 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

I. Formal Matters

Applicants thank the Examiner for entering the Preliminary Amendments filed on October 24, 2001, and September 3, 2002, into the record.

II. Information Disclosure Statement

In response to the Examiner's assertion that the BLAST results cited in the Information Disclosure Statement submitted on March 25, 2002 are not in proper format, including author and accession number, Applicants file herewith, an Information Disclosure Statement listing each reference of the "Blast Search" separately and including authors/inventors, relevant accession numbers and publication dates. Applicants respectfully request that the listed information be considered by the Examiner and be made of record in the above-identified application.

III. Specification

The title was objected to as being non-descriptive. The foregoing amendment, which replaces the original title with a new, descriptive title is believed to overcome this objection.

As requested by the PTO, Applicants have reviewed the application and deleted all references to embedded hyperlinks and/or browser-executable code. Further, the ATCC address on page 372, line 34, has been amended and the paragraph beginning at page 374, line 32, has been amended to comply with the provisions of the Budapest Treaty.

IV Claim Objections

The Examiner suggested that the syntax of Claims 58-77 could be improved by replacing the phrase "shown in Figure 79 (SEQ ID NO:216)" or "shown in Figure 78 (SEQ ID NO:215)" with "of SEQ ID NO:216" or "of SEQ ID NO:215." The claims have been amended as suggested by the Examiner. Accordingly, withdrawal of the claim objections is respectfully requested.

V. Utility Under 35 U.S.C. §101

The Examiner has acknowledged that the PRO846 polypeptide tested positive in the Retinal Neuronal Survival Assay (Assay #52), the Rod Photoreceptor Survival Assay (Assay #56), and the Induction of Endothelial Cell Apoptosis Assay (Assay #109). The Examiner asserts, however, that utility is provided solely by Assay #56, the Rod Photoreceptor Survival Assay, although no explanation is provided as to why this is so. (Applicants note that although the Examiner states that utility is provided by Assay 109, the subsequent discussion of enablement refers only to the Rod Photoreceptor Survival Assay (Assay #56); thus Applicants presume that the Examiner meant to indicate Assay #56 as providing utility). Applicants respectfully submit that both the Retinal Neuronal Survival Assay (Assay #52) and the Induction of Endothelial Cell Apoptosis Assay (Assay #109) also provide patentable utility for the PRO846 polypeptide and the claimed nucleic acids that encode it.

The Legal Standard for Utility

According to 35 U.S.C. § 101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson*[1] the Supreme Court held that the *quid pro quo* contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, i.e. a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[3]

Later, in *Nelson v. Bowler*[4] the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

In *Cross v. Iizuka*[6] the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between."[7] The court perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "in vitro testing, may establish a practical utility."[8]

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[1] *Brenner v. Manson*, 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

Furthermore, M.P.E.P. §2107.03 (III) states that:

> "If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process."

Thus, the legal standard recognizes that *in vitro* or animal model data is acceptable to establish utility as long as the data is "reasonably correlated" to the pharmacological utility described.

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[9] The PTO has the initial burden to prove that applicants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[11], [12]

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

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[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[10] *Ibid.*

[11] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[12] *See also In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 U.S.P.Q. 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 U.S.P.Q. 209, 212-13 (C.C.P.A. 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines")[15], which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility."[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Proper Application of the Legal Standard

As discussed above, the Examiner has stated that patentable utility under 35 U.S.C. §101 is provided by the Rod Photoreceptor Survival Assay. Applicants respectfully submit that at least one specific, substantial and credible utility for the PRO846 polypeptide (and the claimed nucleic acids that encode it) is also provided by the Retinal Neuronal Survival Assay (Assay #52) described in Example 110.

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[15] 66 Fed. Reg. 1092 (2001).

[16] M.P.E.P. §2107.01.

[17] M.P.E.P. §2107 II (B)(1).

The assay described in Example 110 was performed as follows: Sprague Dawley rat pups at postnatal day 7 (mixed population: glia and retinal neuronal types) were killed by decapitation following CO_2 anesthesia and the eyes were removed under sterile conditions. The neural retina was dissected away from the pigment epithelium and other ocular tissue and then dissociated into a single cell suspension using 0.25% trypsin in Ca^{2+}, Mg^{2+}-free PBS. The retinas were incubated at 37°C for 7-10 minutes after which the trypsin was inactivated by adding 1 ml soybean trypsin inhibitor. The cells were plated at 100,000 cells per well in 96 well plates in DMEM/F12 supplemented with N_2 and with or without the specific test PRO polypeptide. Cells for all experiments were grown at 37°C in a water saturated atmosphere of 5% CO_2. After 2-3 days in culture, cells were stained with calcein AM, then fixed using 4% paraformaldehyde and stained with DAPI for determination of total cell count. The effect of various concentrations of PRO polypeptides was reported herein where percent survival is calculated by dividing the total number of calcein AM positive cells at 2-3 days in culture by the total number of DAPI-labeled cells at 2-3 days in culture. Anything above 30% survival was considered positive.

It was well known at the time of the instant application's earliest priority date that the survival-promoting effects of various molecules could be studied using the survival assay described in Example 110. (See Bozyczko-Coyne *et al., J. Neurosci Methods.* 50(2):205-216 (November, 1993); copy enclosed).

The assay described in Example 110 is a highly sensitive cytotoxicity assay. The viability of retinal neuron cells is determined, in the presence and absence of the test substance, based upon the hydrolysis by live cells of membrane-permeable calcein to membrane-impermeable fluorescent calcein. Calcein is a fluorogenic esterase substrate that is hydrolyzed to a green-fluorescent product. The green fluorescent product is an indicator of cellular esterase activity and intact membranes, signifying cell viability.

Otori *et al.* describes essentially the same assay that is described in Example 110. (Otori *et al., Invest Ophthalmol Vis Sci.* 39(6): 972-981 (1998) - copy enclosed). In Otori *et al.*, the effects of glutamate on rat retinal ganglion cells (RGCs) were investigated. The viability of the rat retinal ganglion cells were measured by calcein AM staining after 3 days in culture. The authors found that glutamate caused a dose-dependent increase in RGC death after 3 days in culture. Glutamate in the eye has been implicated in the death of RCGs characteristic of glaucoma.

In another reference by Otori *et al.*, also using calcein AM staining to measure the RGC survival, the authors found that nilvadipine, a dihydropyridine-type calcium channel blocker, prevented glutamate neurotoxicity in RGCs and enhanced RGC survival. (Otori *et al., Brain Res.* 961(2): 213-219 (2003) - copy enclosed). Calcium channel blockers had also been reported to produce favorable effects on the visual prognosis in normal-tension glaucoma; thus the results of Otori *et al.* confirm that the assay described therein and in the instant specification is correlated to a real-world pharmacological utility.

Similarly, PRO846 was found to enhance the survival of retinal neuron cells. Thus, Applicants respectfully submit that a variety of real-life utilities, such as the treatment of retinal disorders, are envisioned for PRO846 based on the retinal neuron survival assay results disclosed herein.

Applicants further submit that the Induction of Endothelial Cell Apoptosis Assay (Assay #109), described in Example 132, also provides patentable utility for the PRO846 polypeptide.

This assay is designed to test the ability of PRO846 to induce apoptosis in endothelial cells. As described in Example 132 of the present application, the ability of PRO846 to induce apoptosis in endothelial cells was tested in human venous umbilical vein endothelial cells (HUVEC, Cell Systems). HUVEC cells were plated on a 96-well plate and were grown for 24 hours before adding test samples containing various polypeptides. Wells without cells were used as a blank and wells with cells only (no polypeptides) were used as a negative control. As a positive control, 1:3 serial dilutions of 50 μl of a 3x stock of staurosporine were used. The cells were incubated for 24 to 35 hours prior to determination of levels of apoptosis using ELISA. The PRO846 polypeptide tested positive in this assay, indicating its ability to induce apoptosis in endothelial cells, and thereby demonstrating its utility in the treatment of several conditions associated with undesired endothelial cell growth, including, for example, the inhibition of tumor growth.

Applicants submit that at the effective filing date of the present application, it was well established that a rate-limiting step in solid tumor growth is the ability to recruit blood vessels from the host tissue. (Benjamin *et al. Proc. Natl. Acad. Sci. USA* 94(16): 8761-8766 (1997) - copy enclosed).

Therefore, Benjamin *et al.* suggest that angiogenesis has become a major target for antitumor therapy on the premise that limiting angiogenesis would retard tumor growth and would inhibit the metastatic spread of tumor cells.[18]

Applicants further submit that at the effective filing date of the present application, it was well-established in the art that endothelial cell apoptosis is closely correlated with the regression or inhibition of tumor growth. For example, as summarized by Benjamin *et al.* in 1997, VEGF is a potent angiogenic factor mediating developmental, physiological, and pathological neovascularization. It was known in the art that the inhibition of VEGF production or function leads to inhibition of tumor growth. Benjamin *et al.* showed that withdrawal of VEGF resulted in regression of newly formed tumor vessels, suggesting that VEGF is required for the maintenance of newly formed tumor vessels. In addition, the authors showed that regression of tumor vessels involved endothelial cell detachment. It is well established that cells that lose contact with their extracellular matrix undergo apoptosis. Based on these findings, Benjamin *et al.* concluded that detachment of the endothelium was the primary effect of VEGF loss and preceded endothelial cell apoptosis. Accordingly, Benjamin *et al.* suggested that the finding that VEGF is required for the maintenance of immature/remodeling tumor vessels may be exploited to increase the efficiency of anti-angiogenesis tumor therapy.

Additional references further confirm that factors that induce endothelial cell apoptosis *in vitro* or *in vivo* are useful in treating cancer. For example, Jiang *et al.* examined the anti-cancer activity of selenium (Se). (Jiang *et al.*, *Mol Carcinog.* 26(4): 213-225 (1999) - copy enclosed). It was known in the art that the trace element nutrient selenium (Se) possessed cancer-preventive activity in both animal models and humans. Jiang *et al.* therefore, examined the effects of chemopreventive levels of Se on the intra-tumoral microvessel density and the expression of vascular endothelial growth factor in 1-methyl-1-nitrosourea-induced rat mammary carcinomas and on the proliferation and survival and matrix metalloproteinase activity of human umbilical vein endothelial cells *in vitro*. The results indicated that increased Se intake as Se-enriched garlic, sodium selenite, or Se-methylselenocysteine led to a significant reduction of intra-tumoral microvessel density in mammary carcinomas, irrespective of the manner by which Se was provided.

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[18] *Id. at 8761.*

Meanwhile, direct exposure of human umbilical vein endothelial cells (HUVEC cells) to Se induced cell death predominantly through apoptosis. Based on these results, Jiang *et al.* suggested that Se metabolites may inhibit the key attributes (proliferation, survival, and matrix degradation) of endothelial cells critical for angiogenic sprouting.

The above references suggest that at the effective filing date of the present invention, human umbilical vein endothelial cells (HUVEC cells) had been used as a reliable system to select novel anti-tumor therapeutic agents based on their effect on the survival of the endothelial cells. Further, induction of the apoptosis of HUVEC cells was considered in the art to be closely related to anti-tumor ability. Thus, Applicants respectfully submit that a variety of real-life utilities, such as inhibition of tumor growth, are envisioned for PRO846 based on the induction of endothelial cell apoptosis assay results disclosed herein.

Accordingly, Applicants submit that in addition to the Rod Photoreceptor Survival Assay (Assay #56), both the Retinal Neuronal Survival Assay (Assay #52) and the Induction of Endothelial Cell Apoptosis Assay (Assay #109) demonstrate that PRO846 has real-world therapeutic uses, including use in inhibition of tumor growth and treating retinal disorders. Thus these two assays also provide patentable utility for the PRO846 polypeptide and the claimed nucleic acids that encode it.

VI. Rejections under 35 U.S.C. 112, First Paragraph (Enablement)

A. Claims 58-77 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

Applicants respectfully submit that Claims 66-67 and 71-73 have been canceled by amendment herein; thus the rejection as it pertains to these claims is moot.

The Examiner has acknowledged that the Rod Photoreceptor Survival Assay (Assay #56), provides patentable utility for the PRO846 polypeptide (and hence for the claimed antibodies that bind it), but asserts that this assay does not provide enablement for the claimed invention.

The Examiner asserts that the main issue to be considered is "whether this assay is predictive of efficacy in treatment of retinal disorders associated with loss of rod photoreceptors." (Page 3 of the instant Office Action).

The Examiner further asserts that the specification has not demonstrated that the models used are art-accepted, and cites Streichert *et al.* in support of the assertion that "art-accepted models use systems in which the rod photoreceptors degenerate, similar to the disease situation giving significance to the increase in survival." (Page 3 of the instant Office Action).

Applicants respectfully direct the Examiner's attention to the enclosed reference by Fontaine *et al.* (*J. Neurosci.* 18(23):9662-9672 (December 1998)) which describes essentially the same assay that is described in Example 111. Fontaine *et al.* demonstrate that it was well known in the art that normal, untreated photoreceptors degenerate rapidly *in vitro* (page 9667, col. 2). While the mutant photoreceptors used in the experiments of Streichert *et al.* degenerate more rapidly than normal photoreceptors, the fact that normal photoreceptors also degenerate *in vitro* makes them an equally valid model for testing agents for their ability to enhance photoreceptor cell survival.

The Examiner asserts that "the instant assay only measures percent survival from a mixed population of first generation tissue culture cells" and questions whether this is an art-accepted model of any disease state. (Page 3 of the instant Office Action). Applicants respectfully point out that Streichert *et al.*, cited by the Examiner, used a dissociated retinal cell culture (pages 476-477) that is essentially the same as that described in Example 111 of the instant specification. This population of first generation tissue culture cells was used to test the effects of factors on rod cell survival *in vitro* (pages 483-484). Thus Streichert *et al.* confirm that the tissue culture cells used in the assay described in the instant specification are an art-accepted model for the study of retinal disorders.

The Examiner further asserts that "it is unclear how enhancing survival can treat a potentially large list of diseases," because the specification allegedly "does not disclose but a couple disorders which can potentially be treated, with no demonstration of any treatment being performed." (Page 3 of the instant Office Action). Applicants respectfully note that it is not necessary to assert or demonstrate that the PRO846 polypeptide can be used to treat all possible eye disorders. If PRO846 could only be used to treat retinitis pigmentosum or AMD, the two disorders specifically cited in Example 110, that would be more than sufficient to demonstrate utility and enablement for PRO846, and the claimed antibodies that bind it. Furthermore, as discussed above, it is well established that evidence of treatment in humans is not required to demonstrate utility. M.P.E.P. §2107.03 (III) states that:

> "If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process."

Thus, the legal standard recognizes that *in vitro* or animal model data is acceptable to establish utility as long as the data is "reasonably correlated" to the pharmacological utility described.

The Examiner further asserts that "[t]he protein of the invention has not been shown to regenerate or grow neurons, simply to keep them from dying," which the Examiner argues "would not appear to be necessary to treat eye disorders since, if the neurons were already present, increasing their survival would not affect the neurons if they were properly functioning in the first place." The Examiner concludes that "[g]rowth of new neurons would appear to be required." (Page 4 of the instant Office Action).

Applicants respectfully point out that it was well known in the art at the time of filing, as disclosed, for example, by Fontaine *et al.*, that photoreceptors (PRs) degenerate in number of conditions, including genetic diseases, light damage, or as a result of normal aging. Fontaine *et al.* note that "PR rescue or **neuroprotection** are topics of great current interest that are **necessary for formulating therapeutic approaches**" (page 9662, col. 1, emphasis added). Thus Fontaine *et al.* confirms that agents which promote survival of photoreceptors are useful in therapeutic approaches to eye disorders, without needing to promote growth of new neurons. Applicants further note that both references cited by the Examiner are directed to the study of photoreceptor survival, not new growth. Petters *et al.*, for example, state that "antiapoptotic agents have been suggested as a **potential therapeutic for the prevention of rod loss**" (page 965, col. 1; emphasis added), providing further confirmation of the utility of agents that promote photoreceptor survival as therapeutics for eye disorders.

Accordingly, one of ordinary skill in the art would recognize that the assay described in Example 111 of the instant specification is an art-accepted model for retinal photoreceptor function, and that positive results in this assay are reasonably correlated to pharmacological utility in the treatment of retinal disorders. Thus, based upon the demonstrated positive results in this assay, one of skill in the art would clearly understand how to use the PRO846 polypeptide in the treatment of retinal disorders.

Applicants further submit that the retinal neuron survival assay described in Example 110 is also an art-accepted model for retinal neuron function, and that positive results in this assay are reasonably correlated to pharmacological utility in the treatment of retinal disorders.

Applicants respectfully point out that many eye disorders are caused not by "malfunctioning" neurons, but by the progressive death of neurons, causing a gradual deterioration of vision as more neurons die. Agents which can keep more neurons from dying are clearly of use in halting the progress of a degenerative eye disease such as glaucoma. Otori *et al.*, (2003) for example, states that calcium channel blockers "are of great clinical interest for patients with normal-tension glaucoma" and that favorable effects on the visual prognosis have been reported (page 213, col. 2). Otori *et al.* report that the calcium channel blocker nilvadipine is able to prevent glutamate neurotoxicity in purified retinal ganglion cells and enhance retinal ganglion cell survival (see Abstract). Otori *et al.* describes essentially the same assay that is described in Example 110, demonstrating that this assay is art-accepted as a model to study potential therapeutic agents for the treatment of eye diseases such as glaucoma. Levin *et al.* (*Invest Ophthalmol Vis Sci.* 37: 2744-2749 (1996)) used a similar *in vitro* retinal ganglion survival assay to study the effects of the 21-aminosteroid tirilizad mesylate. The authors note that ongoing clinical studies of 21-aminosteroids in brain and spinal cord trauma was based upon *in vitro* study of the effects of these agents on neuronal survival (page 2748, col. 2), again confirming that *in vitro* neuronal survival assays are relevant to clinical utility.

Accordingly, one of ordinary skill in the art would recognize that the assay described in Example 110 of the instant specification is an art-accepted model for retinal neuron function, and that positive results in this assay are reasonably correlated to pharmacological utility in the treatment of retinal disorders. Thus, based upon the demonstrated positive results in this assay, one of skill in the art would clearly understand how to use the PRO846 polypeptide in the treatment of retinal disorders.

Applicants further submit that, as discussed above, the Induction of Endothelial Cell Apoptosis Assay (Assay #109), described in Example 132, is an art-accepted model for the selection of anti-tumor agents, and that positive results in this assay are reasonably correlated to pharmacological utility in the treatment of tumors. As discussed above, HUVEC cells were known at the effective filing date to be an art accepted system to select novel anti-tumor therapeutic agents based on their effect on the survival of the endothelial cells.

Further, induction of apoptosis of HUVEC cells was considered in the art to be closely correlated with anti-tumor ability. Thus, Applicants respectfully submit that a variety of real-life utilities, such as inhibition of tumor growth, are envisioned for PRO846 based on the induction of endothelial cell apoptosis assay results disclosed herein, and that one of skill in the art would clearly understand how to use the PRO846 polypeptide in the treatment of tumors.

Accordingly, Applicants respectfully submit that the specification provides enablement for the PRO846 polypeptide and the claimed nucleic acids that encode it.

B. The Examiner asserts that "the specification, while being enabling for SEQ ID NO:215 and 216, does not reasonably provide enablement for polynucleotides or polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity to SEQ ID NO:215 or 216." (Page 4 of the instant Office Action). The Examiner further asserts that "[t]here is no functional limitation in the claims, nor have Applicants taught which regions of the encoded polypeptide are required to maintain any function of this protein." (Page 4 of the instant Office Action).

Applicants note that Claims 66-67 and 71-73 have been canceled by amendment herein; thus the rejection as it pertains to these claims is moot.

The specification provides the nucleic acid sequence of SEQ ID NO:215, which encodes SEQ ID NO:216, as well as the full-length coding sequence of SEQ ID NO:215, and the full-length coding sequence of cDNA deposited under ATCC accession number 209847. The specification further provides the amino acid sequence of the polypeptide of SEQ ID NO:216, with or without its signal sequence. Thus the subject matter of Claims 63-65 and 68-70 is clearly enabled by the specification.

As amended herein, all genus claims have been amended to recite that "the polypeptide enhances the survival of rod photoreceptor cells," (Claims 58-62), "the polypeptide enhances the survival of retinal neuron cells" (newly added Claims 78-82) or "the polypeptide induces apoptosis in endothelial cells " (newly added Claims 783-87). Thus the recited variant nucleic acids all encode polypeptides having the same functions as the polypeptide of SEQ ID NO:216, and can be used in the same manner.

Example 110 of the present application provides the protocol for the retinal neuron survival assay.

By following the disclosure in the specification, one skilled in the art can easily test whether an encoded variant PRO846 polypeptide enhances the survival of retinal neuron cells. Example 111 of the present application provides the protocol for the rod photoreceptor survival assay. By following the disclosure in the specification, one skilled in the art can easily test whether an encoded PRO846 polypeptide enhances the survival of rod photoreceptor cell. Example 132 of the present application provides the protocol for the induction of endothelial cell apoptosis assay. By following the disclosure in the specification, one skilled in the art can easily test whether an encoded PRO846 polypeptide induces apoptosis in endothelial cells.

The specification further describes methods for the determination of percent identity between two amino acid sequences (See pages 122, line 34 to page 125, line 37). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 180, line 10, to page 183, line 8). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 182). Accordingly, one of skill in the art could identify whether a variant PRO846 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making the amino acid sequences (see page 180, line 9 to page 184, line 35) and methods of preparing the PRO polypeptides (see page 185, line 36 and onward). Methods of isolating nucleic acid sequences encoding PRO polypeptides and polypeptide variants are described in the specification at, for example, page 185, lines 10-35; page 190, line 32, to page 191, line 8; and page 135, lines 7-21.

Furthermore, Applicants respectfully submit that it is not necessary for the Applicants to provide which amino residues could be altered to maintain the functional characteristics of the encoded protein. Enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive."[19] Applicants have described three assays in Examples 110, 111 and 132, which provide clear and detailed experimental protocols that could be used by one skilled in the art to determine whether a polypeptide has any of the claimed functions.

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[19] *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert denied,* 480 U.S. 947(1987).

Coupled with the general knowledge in the art at the time of the invention, Applicants submit that the present application provides sufficient guidance to one skilled in the art to use the invention without undue experimentation. As the M.P.E.P. states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.[20]

Accordingly, withdrawal of the enablement rejections under 35 U.S.C. §112, first paragraph, is respectfully requested.

VII. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 58-77 are rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. In particular, the Examiner asserts that "in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus" of nucleic acids encoding polypeptides having at least 80% sequence identity to SEQ ID NO:216. (Page 5 of the instant Office Action).

Applicants note that Claims 66-67 and 71-73 have been canceled by amendment herein; thus the rejection as it pertains to these claims is moot.

The specification clearly discloses the polypeptide of SEQ ID NO:216, both with and without its signal peptide sequence, as well as the nucleic acid sequence of SEQ ID NO:215. The Examiner has acknowledged that polypeptides comprising the amino acid sequence set forth in SEQ ID NO:216, or encoded by SEQ ID NO:215, meet the written description requirement of 35 U.S.C. §112, first paragraph. (See page 6 of the instant Office Action). Thus the written description rejection does not apply to Claims 63-65 and 68-70.

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[20] *In re Certain Limited-charge cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983), *aff'. sub nom., Massachusetts Institute of Technology v A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985) M.P.E.P. 2164.01.

As amended herein, all genus claims have been amended to recite that "the polypeptide enhances the survival of rod photoreceptor cells," (Claims 58-62), "the polypeptide enhances the survival of retinal neuron cells" (newly added Claims 78-82) or "the polypeptide induces apoptosis in endothelial cells " (newly added Claims 783-87).

Example 110 of the present application provides the protocol for the retinal neuron survival assay. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO846 polypeptide enhances the survival of retinal neuron cells. Example 111 of the present application provides the protocol for the rod photoreceptor survival assay. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO846 polypeptide enhances the survival of rod photoreceptor cells. Example 132 of the present application provides the protocol for the induction of endothelial cell apoptosis assay. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO846 polypeptide induces apoptosis in endothelial cells.

The specification further describes methods for the determination of percent identity between two amino acid sequences (See pages 122, line 34 to page 125, line 37). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 180, line 10, to page 183, line 8). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 182). Accordingly, one of skill in the art could identify whether a variant PRO846 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making the amino acid sequences (see page 180, line 9 to page 184, line 35) and methods of preparing the PRO polypeptides (see page 185, line 36 and onward). Methods of isolating nucleic acid sequences encoding PRO polypeptides and polypeptide variants are described in the specification at, for example, page 185, lines 10-35; page 190, line 32, to page 191, line 8; and page 135, lines 7-21.

As noted by the Examiner, factors to be considered in evidencing possession of a claimed genus include "disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. (Page 5 of the instant Office Action).

As discussed above, Applicants have recited structural features, namely, 80% sequence identity to the polypeptide of SEQ ID NO:216, which are common to the genus. Applicants have also provided guidance as to how to make the recited nucleic acids encoding variants of SEQ ID NO:216, including listings of exemplary and preferred sequence substitutions. The genus of claimed nucleic acids is further defined by having a specific functional activity for the encoded polypeptide, either ability to enhance the survival of retinal neuron cells, ability to enhances the survival of rod photoreceptor cells or ability to induce apoptosis in endothelial cells. Accordingly, a description of the claimed genus has been achieved.

Therefore, withdrawal of the written description rejections under 35 U.S.C. §112, first paragraph, is respectfully requested.

VIII. Claim Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 58-77 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. In particular, the Examiner asserts that the recitations of an "extracellular domain," or "the extracellular domain ... lacking its associated signal sequence" are indefinite.

Without acquiescing to the propriety of this rejection and solely in the interest of expedited prosecution in this case, Applicants have canceled Claims 66 and 67, and have amended Claims 58-63 (and, as a consequence, those claims dependent from the same) so as to no longer recite an "extracellular domain," or "the extracellular domain ... lacking its associated signal sequence."

The Examiner has further asserted that Claims 71-73 are vague and indefinite because the claims do not recite conditions for hybridization.

Without acquiescing to the propriety of this rejection and solely in the interest of expedited prosecution in this case, Applicants have canceled Claims 71-73; thus the rejection of these claims is moot.

Accordingly, one skilled in the art would exactly know what the scope of the invention is, and withdrawal of the rejections under 35 U.S.C. §112, second paragraph, is respectfully requested.

IX. Claim Rejections Under 35 U.S.C. §102

Claims 71-73 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Jones *et al.* (Accession No. U70073).

The Examiner asserts that Jones *et al.* teach a polynucleotide which is 20.5% identical to SEQ ID NO:215 and is 97.9% identical to SEQ ID NO:215 over 580 bases, and that this polynucleotide would be expected to hybridize to SEQ ID NO:215 even under the most stringent conditions.

Without acquiescing to the propriety of this rejection and solely in the interest of expedited prosecution in this case, Applicants have canceled Claims 71-73; thus the rejection of these claims is moot.

Accordingly, withdrawal of the rejection under 35 U.S.C. §102(b) over Jones *et al.* is respectfully requested.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39780 –2630 P1C69**).

Respectfully submitted,

Date: September 16, 2005

By: _____
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